

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C. 20231
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 24 October 2000 (24.10.00)	
International application No. PCT/US00/04699	Applicant's or agent's file reference 117-309
International filing date (day/month/year) 25 February 2000 (25.02.00)	Priority date (day/month/year) 26 February 1999 (26.02.99)
Applicant TAN, Yin, Hwee et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

21 September 2000 (21.09.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Antonia Muller

Telephone No.: (41-22) 338.83.38

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
31 August 2000 (31.08.2000)

PCT

(10) International Publication Number
WO 00/50064 A3

(51) International Patent Classification⁷: **A61K 38/21**,
A61P 31/14 // (A61K 38/21, 31:365) (A61K 38/21,
31:4164) (A61K 38/21, 31:517) (A61K 38/21, 31:13)
(A61K 38/21, 31:505) (A61K 38/21, 31:7052)

(21) International Application Number: PCT/US00/04699

(22) International Filing Date: 25 February 2000 (25.02.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/121,931 26 February 1999 (26.02.1999) US
60/181,068 8 February 2000 (08.02.2000) US

(71) Applicant (*for all designated States except US*): INSTITUTE OF MOLECULAR AND CELL BIOLOGY
[SG/SG]; 30 Medical Drive, Singapore 117609 (SG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): TAN, Yin, Hwee
[CA/SG]; 30 Medical Drive, Singapore 117609 (SG).
DRISCOLL, John, S. [US/US]; 4 Infield Court South,
Rockville, MD 20854 (US).

(74) Agent: WILSON, Mary, J.; Nixon & Vanderbye P.C.,
Suite 800, 1100 North Glebe Road, Arlington, VA 22201-
4714 (US).

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE,
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,
MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,
SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ,
VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

(88) Date of publication of the international search report:
5 April 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SYNERGISTIC COMBINATION FOR TREATMENT OF VIRAL-MEDIATED DISEASES

(57) Abstract: Flavivirus and rhabdovirus infections may be treated by administering an interferon such as interferon $\alpha 2$, interferon $\alpha 8$ or interferon β and at least one compound selected from 5-membered cyclic nucleosides, mycophenolic compounds, imidazole derivatives, aminoadamantanes and 2, 4-diaminopyrimidines.

WO 00/50064 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/04699

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/21 A61P31/14 //(A61K38/21,31:365),(A61K38/21,
31:4164),(A61K38/21,31:517),(A61K38/21,31:13),(A61K38/21,31:505),
(A61K38/21,31:7052)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 676 942 A (TESTA DOUGLAS ET AL) 14 October 1997 (1997-10-14)	1-11,20, 21
Y	the whole document, especially column 5 line 24-line 47	1-11,20, 21
Y	--- NEYTS J ET AL: "Use of the yellow fever virus vaccine strain 17D for the study of strategies for the treatment of yellow fever virus infections." ANTIVIRAL RESEARCH, vol. 30, no. 2-3, 1996, pages 125-132, XP000946359 ISSN: 0166-3542 the whole document --- -/--	1-11,20, 21



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

14 December 2000

Date of mailing of the international search report

03. 01. 2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stein, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/04699

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 380 879 A (SJOGREN ERIC B) 10 January 1995 (1995-01-10) cited in the application the whole document ---	1-11,20, 21
Y	ANDREI G. ET AL: "Molecular approaches for the treatment of hemorrhagic fever virus infections." ANTIVIRAL RESEARCH, (1993) 22/1 (45-75). , XP000971421 the whole document, especially page 53 line 25-page 63 line 19 ---	1-11,20, 21
Y	HOLY A ET AL: "STRUCTURE-ACTIVITY STUDIES ON OPEN-CHAIN ANALOGUES OF NUCLEOSIDES: INHIBITION OF S-ADENOSYL-L-HOMOCYSTEINE HYDROLASE AND ANTIVIRAL ACTIVITY. 1.NEUTRAL OPEN-CHAIN ANALOGUES" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, ACADEMIC PRESS, LONDON, GB, vol. 50, 1985, pages 245-261, XP000960342 ISSN: 0010-0765 the whole document ---	1-11,20, 21
Y	ARROYO J I ET AL: "EFFECT OF HUMAN GAMMA INTERFERON ON YELLOW FEVER VIRUS INFECTION" AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE, vol. 38, no. 3, 1988, pages 647-650, XP000946332 ISSN: 0002-9637 the whole document ---	1-11,20, 21
Y	DE CLERCQ E ET AL: "ANTIVIRAL ACTIVITIES OF 5-ETHYNYL-1-BETA-D-RIBOFURANOSYLIMIDAZOLE- 4-CARBOXAMIDE AND RELATED COMPOUNDS" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 35, no. 4, 1991, pages 679-684, XP000971464 ISSN: 0066-4804 the whole document ---	1-11,20, 21
X	WO 98 19670 A (NAJARIAN THOMAS) 14 May 1998 (1998-05-14) the whole document, especially page 6 line 5-line 20 ---	1-11,20, 21
A	US 4 975 434 A (MARQUEZ VICTOR E ET AL) 4 December 1990 (1990-12-04) cited in the application the whole document ---	1-11,20, 21
	--- -/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/04699

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages.	Relevant to claim No.
A	<p>DRISCOLL J S ET AL: "CYCLOPENTENYL CYTOSINE A NEPLANOCIN ANALOGUE WITH PRECLINICAL ANTITUMOR AND ANTIVIRAL ACTIVITY" PROCEEDINGS AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 28, 1987, page 328 XP000946357 ISSN: 0197-016X the whole document</p>	1-11,20, 21
A	<p>FOSTER G R ET AL: "DIFFERENT RELATIVE ACTIVITIES OF HUMAN CELL-DERIVED INTERFERON- ALPHA SUBTYPES: IFN-ALPHA8 HAS VERY HIGH ANTIVIRAL POTENCY" JOURNAL OF INTERFERON AND CYTOKINE RESEARCH,US,MARY ANN LIEBERT, NEW YORK, NY, vol. 16, no. 12, 1996, pages 1027-1033, XP000876621 ISSN: 1079-9907 the whole document</p>	1-11,20, 21
A	<p>EP 0 331 080 A (YAMASA SHOYU KK ;SUMITOMO PHARMA (JP)) 6 September 1989 (1989-09-06) cited in the application the whole document</p>	1-11,20, 21
A	<p>GB 1 135 898 A (DAVOLL JOHN) 4 December 1968 (1968-12-04) the whole document</p>	1-11,20, 21
A	<p>HYNES JB ET AL: "Quinazolines as inhibitors of dihydrofolate reductase. 4. Classical analogues of folic and isofolic acids" JOURNAL OF MEDICINAL CHEMISTRY, vol. 20, no. 4, 1977, pages 588-591, XP002155519 the whole document</p>	1-11,20, 21
E	<p>WO 00 15210 A (KWONG ANN ;VERTEX PHARMA (US); TUNG ROGER (US)) 23 March 2000 (2000-03-23) the whole document</p>	1-11,20, 21
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/04699

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>J A FINDOR ET AL: "AMANTADINE HCL ALONE AND ASSOCIATED WITH RECOMBINANT ALPHA IFN 2a DURING A SHORT TERM THERAPY IN CHRONIC HCV INFECTION" HEPATOLOGY,US,WILLIAMS AND WILKINS, BALTIMORE, MD, vol. 26, no. 4, 1 October 1997 (1997-10-01), page 217A XP002093941 ISSN: 0270-9139 the whole document</p>	
A	<p>LUSCRI B J: "SYNERGISTIC EFFECTS OF HUMAN INTERFERONS WITH EITHER AMANTADINE OR RIMANTADINE" ABSTRACTS OF THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR, vol. 83, 1983, page A130 XP000946512 1983 ISSN: 0094-8519 the whole document</p>	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/04699

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20 and 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-11, 20, 21 (all partially)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-11,20,21 partially

Antiviral composition comprising interferon in combination with 5-membered cyclic nucleosides for the treatment of flavivirus and rhabdovirus infection.

2. Claims: 1-11,20,21 partially

Antiviral composition comprising interferon in combination with mycophenolic acid for the treatment of flavivirus and rhabdovirus infection.

3. Claims: 1-11,20,21 partially

Antiviral composition comprising interferon in combination with imidazole derivatives for the treatment of flavivirus and rhabdovirus infection.

4. Claims: 1-11,20,21 partially

Antiviral composition comprising interferon in combination with adamantanes for the treatment of flavivirus and rhabdovirus infection.

5. Claims: 1-11,20,21 partially

Antiviral composition comprising interferon in combination with quinazoline derivatives of 2,4-diaminopyrimidine for the treatment of flavivirus and rhabdovirus infection.

6. Claims: 12-19

Interferon alpha8 for the treatment of flavivirus and rhabdovirus infection.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Patent Application No

PCT/US 00/04699

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5676942	A	14-10-1997	US 5503828 A AT 179330 T AU 674306 B AU 3660093 A CA 2129533 A DE 69324671 D EP 0625991 A JP 7503851 T KR 223255 B PL 176408 B RU 2129437 C WO 9316107 A	02-04-1996 15-05-1999 19-12-1996 03-09-1993 19-08-1993 02-06-1999 30-11-1994 27-04-1995 15-10-1999 31-05-1999 27-04-1999 19-08-1993
US 5380879	A	10-01-1995	AU 1916995 A BR 9506820 A CA 2183529 A CN 1143366 A EP 0745074 A FI 963219 A IL 112664 A JP 9509171 T WO 9522535 A US 5441953 A ZA 9501292 A	04-09-1995 09-09-1997 24-08-1995 19-02-1997 04-12-1996 11-10-1996 20-06-1999 16-09-1997 24-08-1995 15-08-1995 16-08-1996
WO 9819670	A	14-05-1998	AU 5157998 A	29-05-1998
US 4975434	A	04-12-1990	AU 5097790 A WO 9009177 A US 4968690 A	05-09-1990 23-08-1990 06-11-1990
EP 0331080	A	06-09-1989	JP 1221388 A JP 1930254 C JP 6060193 B JP 1254697 A JP 2565736 B JP 1254698 A JP 2514830 B CA 1317588 A US 5059590 A US 5126361 A	04-09-1989 12-05-1995 10-08-1994 11-10-1989 18-12-1996 11-10-1989 10-07-1996 11-05-1993 22-10-1991 30-06-1992
GB 1135898	A		NONE	
WO 0015210	A	23-03-2000	AU 6037499 A	03-04-2000

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 117-309	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 04699	International filing date (day/month/year) 25/02/2000	(Earliest) Priority Date (day/month/year) 26/02/1999
Applicant INSTITUTE OF MOLECULAR AND CELL BIOLOGY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.